Five-year Mortality in Elderly French Subjects from the PAQUID Epidemiological Survey: the Burden of Diabetes

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We describe the 5-year mortality and its risk factors in a cohort of elderly people with and without known diabetes mellitus. The PAQUID cohort was representative of the population older than 65 living in Gironde, south-west France. Potential mortality risk factors were collected during a baseline evaluation, using a health questionnaire, from 68.9 % of a randomly selected sample of over-65s in 1988. A total of 237 subjects (8.5 %) had diabetes. Annual review occurred for 5 years and cause of any death was ascertained from family doctors. After 5 years, 623 people (22.3 %) had died, of whom 576 were non-demented; 30.0 % of the diabetic group versus 20.3 % of the non-diabetic group had died. Survival of the known diabetic group was lower than that of the non-diabetic group ($p < 0.001$), although this excess mortality was significant only in the 65 to 75 age range (relative risk 1.8; 95 % confidence interval 1.2 to 2.8, $p = 0.04$). Cardiovascular mortality rate did not differ between the diabetic and non-diabetic groups (RR 1.2 [0.8–2.0]). Death related to neoplasia was significantly higher in the known diabetic group (RR 2.2 [1.2–3.3], $p = 0.01$). In the final model, integrating diabetes as a mortality risk factor in the total cohort, known diabetes at the baseline examination was an independent risk factor for mortality (RR 1.4 [1.0–1.8], $p = 0.01$), in addition to tobacco use, hypertension and functional dependency. These results confirm suggestions that diabetes increases mortality in the over-65 age group, perhaps with an adverse interaction with other pathology.

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Introduction

Excess mortality related to diabetes mellitus is well described (e.g. Croxon *et al.*,[1] De Grauw *et al.*,[2] Lee *et al.*,[3] Knuiman *et al.*,[4] Muggeo *et al.*,[5] Gatling *et al*;[6] see Sinclair *et al.*[7] for review), but the effect diminishes in older populations. We have been following a cohort of elderly people (aged over 65 years) in the PAQUID cohort since 1988.[8] The calculated prevalence of diabetes in this population was 10 %. This cohort allowed us to compare mortality in people with known diabetes with a suitable control group, all living in the same geographical area, in comparable conditions.

The purpose of the present study was to describe 5-year mortality in elderly French people known to be diabetic compared to people not known to be diabetic in a representative sample of the total population and in two age groups, 65–75 years and above 75 years. The underlying cause of death was explored and predictors of mortality, as registered in a baseline (1988) health evaluation, were analysed.

Research Design and Methods

Study Population and Design

The target population of this study consisted of community residents aged 65 years and older on 31 December 1987, living in Gironde (south-western France). A sample of 4050 individuals was selected randomly from the electoral rolls using a three-step procedure stratified by age, sex and size of urban unit. Of the 4050, 1258 refused to participate and 2792 subjects (68.9 %) were visited for baseline screening of the cohort. All underwent a 90-minute interview by a trained psychologist and completed a health questionnaire.

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As previously described,[8] diabetic subjects were identified using three questions of the questionnaire: 'Are you diabetic?' 'Are you on a diabetic diet?' and 'What kind of medications do you take daily?' (seeking hypoglycaemic medications). Subjects were classified as diabetic when two or three items were positive.

Of the 2792 subjects, 237 were classified as having diabetes (males 117 (49.4 %), females 120 (50.6 %)), giving an estimated prevalence for diabetes of 8.5 %. The questionnaire was validated in a sample of 100 elderly people living in an institution and diagnosed according to WHO criteria. The sensitivity was 65.3 % and specificity 98 %. We then excluded demented subjects from the PAQUID sample because the baseline case-finding procedure was based on the responses to the questionnaire and was too subjective. Demented subjects were identified in the PAQUID study using previously described procedure according to DSM III criteria.[9,10] There were 7 in the known diabetic group and 59 in the other subjects.

Baseline Health Questionnaire

Potential mortality risk factors investigated included physical health, symptoms of depression, autonomy, tobacco consumption and treatment regimen. Physical health assessment included measurement of weight and arterial blood pressure (systolic and diastolic), history of painful ischaemic heart disease, painful vascular disease, antecedent stroke, and dyspnoea. For the mortality risk factor study, the definition of hypertension was systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg or treatment with antihypertensive drugs.[11] The French version of the CES-D 20-item scale was used to measure depressive symptomatology. The higher the total score, the higher the level of depressive symptomatology expressed by the respondent; the possible total score ranges from 0 to 60, with higher scores reflecting more symptoms of depression. People were considered depressed when the CES-D was 17 or greater in men and 23 in women.[12] Functional assessment comprised the Katz scale of daily life activities (ADL)[13] and the Lawton scale of instrumental daily life activities (IADL).[14] People were classified as dependent or not according to each scale. They were also classified as current smokers or ex-smokers opposed to non-smokers.

Mortality Assessment

The life status of the elderly cohort gathered in 1988 was ascertained annually by telephone contact prior to a home visit (initial visit, first, third and fifth year) or by a mailed questionnaire (second and fourth year). When a death occurred, a questionnaire was sent to the family doctor to ascertain the date and the cause of death. Complementary information was obtained from the person identified as close to the subject at baseline evaluation. A physician coded the mortality causes according to the International *Classification of Diseases*, 9th revision.[15]

Statistical Analysis

Data were analysed using the BMDP statistical software package.[16] The Kaplan Meyer model with Log Rank test was used to compare global mortality as the dependent variable between known diabetic and other subjects. The relative risks of death were estimated using a Cox proportional hazard model with delayed entry, in which the timescale was the age of the subject. In the study of age-associated events in elderly people, age is the most appropriate variable rather than time since baseline survey.[17,18] This allows direct modelling of the risk of death according to age, which is no longer included as a covariable. The initial sample for study was drawn from people aged 65 or older initially and included people up to age 102 years. The subjects considered for subsequent study were further limited to those who were alive at the time of the baseline evaluation. The sample is thus truncated because subject inclusion is conditional upon the fact that death had not occurred before the study. To deal with the truncation, we used a Cox model with delayed entry where a subject is considered to be at risk of death between the age at entry to the cohort and the age of death. As mortality risk associated with diabetes has been described to decrease with age we performed the analysis on risk factors separately in the age ranges 65–75 years and above 75 years in both the known diabetic and in the other subjects.

Results

During 5 years' follow-up, 623 deaths were registered from 2792 subjects (22.3 %). Life status was known for each subject of the cohort. Forty-seven people with dementia died, of whom 6 were known to have diabetes. In the target population of our study, which excluded demented subjects, 576 deaths were analysed. There were 69 deaths in the known diabetic group (30 % of the initial population) compared to 507 (20.3 %) in the other subjects. Survival was significantly lower in known diabetic subjects than in other subjects according to Kaplan Meyer analysis with Log Rank test ($p < 0.001$, see Figure 1). Analysis of 5-year mortality according to age showed that the excess mortality of diabetic subjects was statistically significant in the 65–75-year age range ($p = 0.04$, Table 1) but not for subjects aged over 75, although the trend was also higher in the diabetic group there.

The higher risk of mortality in the known diabetic group was not significantly associated with the type of diabetes treatment, diet alone (RR 1.1, 95 % CI: 0.5–2.6 $p = 0.84$), oral hypoglycaemic agents (RR 1.1, 95 % CI: 0.7–1.9 $p = 0.68$) or insulin (RR 1.5, 95 % CI: 0.6–4.0 $p = 0.38$).

The main causes of death were cardiovascular diseases

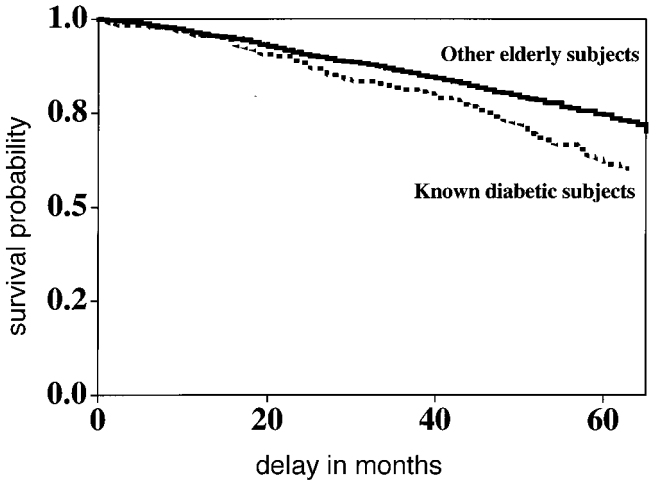

Figure 1. Five-year survival among the known elderly diabetic and the other elderly subjects, compared using a log rank test: $p < 0.001$

Table 2. Distribution of the cardiovascular and neoplastic causes of death in known diabetic and other elderly subjects from PAQUID epidemiological study

	Known diabetic subjects	Other subjects
Number of deaths	69	507
Cardiovascular disease	21	195
Ischaemic heart disease	6	39
Peripheral vascular disease	1	12
Stroke	5	58
Other	9	85
Neoplasia	17	82
Neoplasia from gastrointestinal tract	9	32
Colon	2	11
Stomach	3	7
Liver	2	3
Pancreas	1	8
Other	1	3

and neoplasia (Table 2). The proportion of death of cardiovascular origin was 30.4 % of all mortality in the known diabetic group versus 38.5 % in the other subjects. The global cardiovascular mortality was not statistically different in the known diabetic than in the other subjects (Table 3). Six deaths in the known diabetic group occurred from coronary heart disease (2.6 % of the initial group) versus 39 (2.4 % of the initial group) in other subjects. Fatal stroke rates were also not significantly different between the two groups: 5 (2.2 % of the initial known diabetic group) versus 58 (2.3 % of the initial other subjects; Table 2). Unexpectedly the relative risk for neoplasia-related death was higher in the known diabetic subjects versus the other subjects in the total cohort and in the younger age group (Table 3). Neoplasia-related death accounted for 24.7 % of mortality in the known diabetic group versus 18.7 % in the other subjects, related to an increase in mortality from gastrointestinal tract neoplasia (8 or 11.6 % of total death causes, in the known diabetic subjects versus 33 or 6.5 % in the other subjects), mainly colon, stomach or pancreas, with no difference in distribution between the two groups (Table 2).

Terminal nephropathy accounted for one death in the known diabetic group and two patients not classified at baseline as diabetic died from acute diabetic metabolic disorders. Two suicides occurred in each group. No cause of death was noted in one case from the known diabetic subjects and in five from the other group. The mortality questionnaire filled in by the family practitioner mentioned diabetes only in three of 69 dead known diabetic subjects.

In the age class 65–75 years old at baseline, univariate analysis of the known diabetic population showed only tobacco consumption and dyspnoea as risk factors for

Table 1. Number of deaths during 5-year follow-up of the known elderly diabetic and the other subjects of the PAQUID study, demented subjects excluded. Analysis according to age and sex distribution at baseline evaluation. Relative risks were computed with a Cox model with delayed entry after adjustment for sex

	PAQUID cohort Number of subjects		Number of deaths (% of the initial group)				RR (95 % CI) p value
	Known diabetic subjects (n)	Other subjects (n)	Known diabetic subjects		Other subjects		
			n	%	n	%	
Total	230	2496	69	(30.0)	507	(20.3)	1.5 (1.2–2.0)
Women	117	1513	28	(23.9)	253	(16.7)	$p = 0.003$
Men	113	983	41	(36.3)	254	(25.8)	
65–75 years	129	1317	28	(21.7)	142	(10.8)	1.8 (1.2–2.8)
Women	59	749	8	(13.6)	44	(5.9)	$p = 0.04$
Men	70	568	20	(28.6)	98	(17.2)	
> 75 years	101	1179	41	(40.6)	365	(31.0)	1.3 (0.9–1.9)
Women	58	764	20	(34.5)	209	(27.3)	$p = 0.12$
Men	43	415	21	(48.8)	156	(37.6)	

Table 3. Cardiovascular diseases and neoplasm as underlying causes of 5-year mortality of the known diabetic versus the other elderly subjects in the PAQUID epidemiological study, demented subjects excluded. Relative risks were computed with a Cox model with delayed entry after adjustment for sex

	PAQUID cohort Number of subjects		Number of cardiovascular deaths (% of the initial group)		Number of neoplasm deaths (% of the initial group)	
	Known diabetic subjects	Other subjects	Known diabetic subjects	Other subjects	Known diabetic subjects	Other subjects
Total	230	2496	21 (9.1 %)	195 (7.8 %)	17 (7.4 %)	95 (3.8 %)
Women	117	1513	9 (7.7 %)	92 (6.1 %)	6 (5.1 %)	59 (3.9 %)
Men	113	983	12 (10.6 %)	103 (10.5 %)	11 (9.7 %)	36 (3.7 %)
RR (95 % CI)			1.2 (0.8–2.0) $p = 0.35$		2.0 (1.2–3.3) $p = 0.01$	
Age and sex distribution at baseline evaluation						
65–75	129	1317	9 (7.0 %)	46 (3.5 %)	10 (7.8 %)	44 (3.3 %)
Women	59	749	3 (5.1 %)	11 (1.4 %)	3 (5.0 %)	11 (1.5 %)
Men	70	568	6 (8.6 %)	30 (5.3 %)	7 (10.0 %)	33 (5.8 %)
RR (95 % CI)			1.0 (0.6–1.8) $p = 0.91$		2.1 (1.0–4.2) $p = 0.03$	
> 75	101	1179	12 (12.0 %)	154 (13.1 %)	7 (6.9 %)	33 (2.8 %)
Women	58	764	6 (10.3 %)	81 (10.6 %)	3 (5.2 %)	26 (3.4 %)
Men	43	415	6 (14.0 %)	73 (17.6 %)	4 (9.3 %)	25 (6.0 %)
RR (95 % CI)			1.8 (0.9–3.9) $p = 0.12$		1.8 (0.8–3.9) $p = 0.15$	

mortality ($p = 0.02$ and 0.04, respectively, Table 4). Dyspnoea was related to tobacco consumption, since after multivariate analysis only tobacco consumption remained a significant mortality risk factor. Surprisingly, none of the baseline characteristics examined were identified as risk factors in the known diabetic population above 75 (Table 4). In the other, not diabetic cohort, the risk factor profile was different (Table 4). Male gender ($p < 0.001$), tobacco intake ($P < 0.001$), painful vascular disease ($p = 0.009$), dyspnoea ($p = 0.04$), dependency according to either ADL Katz scale ($p < 0.001$) or IADL Lawton's scale ($p < 0.001$), depressive symptomatology ($p = 0.008$) were identified in the 65–75 years age class by univariate analysis and the final model in this age class identified as independent risk factors male gender ($p = 0.002$), smoking ($p = 0.002$), dependency (Katz: $p < 0.001$, Lawton: $p < 0.001$) and depressive symptomatology ($p = 0.008$). The risk factor profile above 75 years of age in the population classified as 'other' was similar to that observed in the younger population except that painful arterial disease was no longer significant and history of stroke became significant ($p = 0.03$). Independent risk factors in this group were male gender ($p = 0.002$), smoking ($p = 0.008$), hypertension ($p = 0.002$), and IADL Lawton's scale dependency ($p < 0.001$).

In the last model we analysed the mortality-risk factors for the whole PAQUID cohort. The final model confirmed that diabetes was an independent mortality risk factor: RR 1.36 (95 % CI 1.0–1.8, $p = 0.03$). The other independent mortality risk factors were male gender (RR : 1.75 [1.4–2.3], $p < 0.001$), tobacco (RR : 1.6 [1.3–2.1], $p < 0.001$), hypertension (RR : 1.3 [1.1–1.5], $p = 0.01$), and dependency by ADL (RR : 1.3 [1.1–1.6], $p = 0.01$) and IADL (RR : 2.1 [1.7–2.6], $p < 0.001$).

Discussion

In this study of mortality and risk for mortality, the diabetes case-finding procedure was different from that in most other mortality studies,[1,2,4–6] since we selected subjects based on their own knowledge of their health status. We have shown that this is an acceptable selection procedure in the French population.[8] A potential confounder of our data is the initial refusal rate of 31 %. However, the PAQUID non-respondents were similar in age, gender, and educational level to the respondents[19] and the refusal rate was equivalent to that observed in other prevalence studies. Life status data is relatively easy to obtain in France as a death is registered in the administrative area (commune) of birth and diagnosis was probably accurate as information was obtained from family doctors whose information may differ from that on the official death certificate.[20] The percentage (~ 1 %) of undefined cause of death in our study was acceptable. Thus, we believe our case-finding procedure provides an accurate basis for analysing the effects of diabetes in our population.

We observed an excess mortality in elderly known diabetic subjects compared to those not known to have diabetes. This excess did not reach statistical significance in those aged over 75 at baseline, although the trend remained. The relative risk of death in the diabetic population over 65 was dramatically higher (albeit with wide confidence intervals) in a British study, which estimated the risk at 12.1 in 65-year-olds, compared to 1.3 in the over 85s.[1] Trends in mortality evaluated in other studies using the calculation of standardized mortality ratio are concordant with this study for age distribution.[2,4,5] The difference in shortening of life

Table 4. Association between selected baseline characteristics and all causes of 5-year mortality in the known diabetic and the other elderly subjects of the PAQUID cohort: univariate analysis according to the delayed entry multiple regression Cox model in each age class

	Known diabetic subjects				Other subjects			
	65–75 years		> 75 years		65–75 years		> 75 years	
	RR (95 % CI)	*p*	RR (95 % CI)	*p*	RR (95 % CI)	*p*	RR (95 % CI)	*p*
Sex (F/M)	0.4 (0.2–1.1)	0.07	0.6 (0.3–1.3)	0.22	0.3 (0.2–0.5)	< 0.001	0.5 (0.4–0.6)	< 0.001
Weight	1.0 (–)	0.32	1.0 (–)	0.46	1.0 (–)	0.13	1.0 (–)	0.37
Smoker (current and ex) vs non-smoker	2.4 (1.1–5.3)	0.02	1.1 (0.5–2.2)	0.86	3.0 (2.1–4.4)	< 0.001	1.9 (1.5–2.4)	< 0.001
HTA	0.9 (0.4–2.3)	0.92	1.2 (0.5–2.8)	0.72	1.1 (0.8–1.6)	0.42	1.6 (1.2–2.0)	< 0.001
Painful ischaemic heart disease (yes vs no)	1.1 (0.5–2.4)	0.81	1.6 (0.8–3.3)	0.17	1.5 (1.0–2.2)	0.053	1.1 (0.9–1.4)	0.35
Painful vascular disease (yes vs no)	1.1 (0.4–2.8)	0.81	2.0 (0.9–4.4)	0.09	2.0 (1.2–3.3)	0.009	1.3 (0.9–1.8)	0.11
Stroke antecedent	2.5 (0.7–8.7)	0.14	0.7 (0.2–2.2)	0.55	1.3 (0.6–2.6)	0.49	1.5 (1.0–2.3)	0.03
Dyspnoea	2.4 (1.0–5.3)	0.04	1.9 (0.9–3.9)	0.07	1.5 (1.0–2.3)	0.04	1.3 (1.0–1.6)	0.03
Depressive symptomatology	1.0 (0.4–2.4)	0.92	1.8 (0.8–4.0)	0.13	1.8 (1.2–2.7)	0.008	1.5 (1.1–2.0)	0.004
ADL dependency	2.4 (1.0–6.2)	0.06	1.3 (0.6–2.9)	0.46	2.7 (1.7–4.3)	< 0.001	1.4 (1.1–1.8)	0.01
IADL dependency	1.5 (0.7–3.4)	0.30	1.8 (0.8–3.7)	0.13	3.2 (2.2–4.6)	< 0.001	1.8 (1.4–2.2)	< 0.001

expectancy between diabetic and non-diabetic decreased with increasing age.

In contrast to other studies,[2,21] the excess mortality in our French diabetic population could not be attributed to cardiovascular causes. The percentage of cardiovascular causes of death in diabetic people reported in the literature varies according to population from 64 %[2] to 37.8 %.[3] The relative risk of death from cardiovascular disease was 2.0 in two studies involving Type 2 diabetic subjects of any age.[2,6] One possible explanation of our failure to find such an effect in our study could be a lack of recognition of cardiac morbidity, as prevalence of silent myocardial infarction increases with age.[22] Furthermore condition for participating in the PAQUID epidemiological study was to be alive in 1988. This implicates selection of survivors. Excess mortality related to diabetes has been described to be the highest between 60 and 69-years old.[1,7]

The observed increased percentage of deaths attributed to neoplasia in our diabetic cohort was not expected and contrasts with previous diabetes mortality studies.[1,7] The only documented link between the risk of cancer and diabetes has been with liver and pancreas neoplasia in Type 1 diabetes[23] and we did not find an excess in these two cancers in our known diabetic group. It has been suggested that diabetes mellitus may have a deleterious effect on the prognosis of cancer.[24] Muggeo *et al*. have put forward evidence for the impact of poor diabetes control on mortality of patients older than 75 years.[25] Unfortunately we studied only the main cause of death and did not obtain data on other morbidity at the time of death. Mortality risk factor analysis thus seemed more appropriate to describe the impact of a chronic disease on survival in elderly subjects.

Smoking was a powerful mortality risk factor in both known diabetic and other subjects. This effect disappeared in the older diabetic group, probably due to the previous death of the more exposed subjects. Smoking, increasing the risk of cardiovascular and neoplastic diseases, was involved in the excess mortality of the 65–75-year age group and could have a synergistic effect with hyperglycaemia.[26] Dyspnoea in this study was not an independent mortality risk factor. It has been suggested that pulmonary function may be altered in diabetic subjects[27] but this has been disputed.[28] We did not study the underlying cause of dyspnoea, which can also be due to impaired cardiac function. Cardiorespiratory impairment has been described as a risk factor for death in young Type 2 diabetic subjects[29] and dyspnoea is more frequent in elderly diabetic subjects in Gironde.[8] Dyspnoea has been described in another study[30] as a mortality risk factor for both the entire population. It is noteworthy that other mortality risk factors, including functional dependency and depressive symptomatology,[31] although more frequent in this known diabetic population[8] were not identified as having any association with mortality.

We have observed a deleterious effect of diabetes on survival in elderly people. These subjects came from a representative group of elderly subjects living in the south-west region of France receiving usual medical care. It has been shown that attending a diabetes centre is associated with improved survival.[32] This suggests an opportunitiy for intervening to diminish the increased risk of premature death in elderly people with diabetes.

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